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<b>(54) Title:</b> GONADOTROPHINS		
<b>(57) Abstract</b>  The present invention relates to the use of gonadotrophins in the induction of folliculogenesis in anovulatory women. In particular, it relates to the use of LH (or an equivalent dosage of hCG) in the production of a medicament for inducing folliculogenesis in anovulatory women at a specified daily doses. In certain embodiments, LH may be used in conjunction with FSH.		

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### Gonadotrophins

The present invention relates to the use of gonadotrophins in the treatment of anovulatory women. In particular, it relates to the use of luteinising hormone (LH) for promoting follicular development, and especially paucifollicular and monofollicular development, when inducing ovulation in anovulatory women.

Gonadotrophins are widely used in clinical practice to treat women with WHO group II and WHO group I anovulation (World Health Organisation Technical Report 514, (1973)). Conventionally, folliculogenesis is induced by administering hMG (human menopausal gonadotrophin) or u-hFSH (urinary human follicle stimulating hormone) at a dose of 75 – 150 IU/day. This dose is increased after a few days (usually five) by steps of 75 IU. It is rare to exceed 450 IU/day. When there is at least one follicle having a mean diameter of at least 18 mm and no more than two follicles having a mean diameter of at least 16 mm, a high dose (of 5000 IU for example) of hCG (human chorionic gonadotrophin) is administered to induce ovulation. This “conventional protocol” has been used successfully for more than 20 years. It carries some risks however, mainly in patients with polycystic ovarian disease (PCOD). These risks include the occurrence of ovarian hyperstimulation syndrome (OHSS), and a relatively high incidence of multiple pregnancies (Schenker *et al*, *Fertil. Steril.* 35:105-123 (1981)). Although the majority of multiple pregnancies are twins, induction of ovulation contributes to one third of the high rank multiple births in the UK (Levene *et al*, *Br. J. Obstet. Gynaecol.* 99:607-613 (1992)).

Careful monitoring during treatment by ultrasound (US) and assessment of serum oestradiol (E<sub>2</sub>) have reduced these risks but have not been able to prevent them in all patients. These problems are directly related to the difficulty of obtaining the growth of a single dominant follicle leading to non-physiological multifollicular development.

During the last 10 years, a new protocol has been designed (the “chronic low dose

protocol”) and tested in order to reduce further the incidence of the complications of gonadotrophin therapy (Seibel *et al*, *Int. J. Fertil.*, 29:338-339 (1984); Buvat *et al*, *Fertil. Steril.*, 52:553-559 (1989); Hamilton-Fairley *et al*, *Human Reprod.* 6:1095-1099 (1991); Sagle *et al*, *Fertil Steril.*, 55:56-60 (1991); Shoham *et al*, *Fertil. Steril.*, 55:1051-1056 (1991); Meldrum, *Fertil Steril.*, 55:1039-1040 (1991)). This protocol starts with a low dose of FSH or hMG (75 IU/day) and no dose adjustment before seven or preferably 14 days of treatment. If a dose adjustment is required, this is made by incremental steps of only 37.5 IU. In addition, each subsequent increase may only be effected after seven days of treatment at a given dose. The concept of this chronic low dose protocol is to find the threshold amount of FSH necessary to promote unifolliculogenesis. Encouraging results have been published so far, showing that this approach reduces the mean number of preovulatory follicles, the average preovulatory E<sub>2</sub> level and the size of the ovary at mid-luteal phase.

However, despite the use of the chronic low dose protocol, some treatment cycles still have to be cancelled due to an over-response (e.g. where there are more than 3 follicles with a mean diameter of 16 mm or more). In addition, the multiple pregnancy rate, although clearly improved when compared to the conventional protocol, is still higher than in spontaneous conception cycles i.e. 5 – 10 % in induced ovulation as opposed to 1.5 % in spontaneous cycles. This is due to the fact that development of a single pre-ovulatory follicle is obtained in only about two thirds to three quarters of the induced cycles and follicles having a mean diameter of 15 mm or less are usually not considered when assessing the number of pre-ovulatory follicles on the day of hCG administration (Buvat *et al*, *Fertil. Steril.*, 52:553-559 (1989); Hamilton-Fairley *et al*, *Human Reprod.* 6:1095-1099 (1991)). It is however not clear whether follicles with a mean diameter of 14 to 15 mm, or even less, on the day of hCG administration, will ovulate and lead to the release of a healthy fertilisable oocyte. Thus, it would be desirable to have improvements in FSH-induced follicular development treatment in which the rates of multiple pregnancy and cycle cancellation are reduced.

Antral follicle growth is induced by FSH. Continuously throughout life and up to the menopause, some follicles enter a growth phase which is interrupted by regression and atresia before reaching the full maturity stage of preovulatory status (Hillier, *Hum. Reprod.*, 9:181-191 (1994)). During the growth phase, any follicle could be rescued from atresia, provided that it is exposed to a sufficient concentration of FSH. The level of FSH required to prevent atresia and promote further growth of a follicle is called the "FSH threshold" level (Brown, *Aus. NZ J. Obstet. Gynecol.*, 18: 47-55 (1987)). The FSH threshold level varies with time and, at a given time-point, the follicles which are currently in a growth phase have different FSH threshold levels, This is the rationale on which the "chronic low dose" protocol is based. A progressive and cautious increase in the dose of FSH is used for finding the threshold level of a minimal number of follicles, and hopefully achieving mono-ovulation.

It is known that luteinising hormone (LH) also contributes to the phenomenon of follicle dominance and mono-ovulation. Indeed, although some LH is essential for oestrogen synthesis during folliculogenesis, there is evidence that excessive exposure to LH will trigger follicular atresia and suppress granulosa proliferation. Developing follicles appear thus to have finite requirements for stimulation by LH, beyond which normal follicular development ceases. This is the "LH ceiling" concept (Hillier, *Hum. Reprod.*, 9:181-191 (1994)). It is believed that, at a given time-point, the follicles which are currently in a growth phase have different LH ceiling levels. It is suggested that the more mature follicles are more resistant to the atretic action of LH than less mature follicles.

Two cases of WHO group I anovulation treated by either FSH alone or hMG using a step-up protocol have been reported (Glasier *et al*, *Journal of Endocrinology*, 119 A-159 (1988)). The "FSH alone" cycle had a much larger number of mature follicles than the hMG cycle, possibly supporting a role of LH in the atresia of secondary follicles. Afterwards two comparative studies were published. In a first cross-over study in 10 hypogonadotrophic hypogonadal women, a striking difference was

recorded in terms of preovulatory E<sub>2</sub> levels, but follicular count was not reported (Couzinet *et al*, *J. Clin. Endocrinol. Metab.* **66**:552-556 (1988)). A second cross-over study in 9 hypogonadotrophic hypogonadal women reported a mean number of follicles having a mean diameter of more than 16 mm on the day of hCG administration of 2.0 (0.7 in hMG-treated cycles and of 1.2 in FSH-treated cycles (Shoham *et al*, *Fertil. Steril.*, **55**:1051-1056 (1991)). No information is available on the number of smaller follicles.

More recently, the results of administering 150 IU hFSH (human FSH) and 75 IU r-hLH (recombinant human LH) to a single patient with unmeasurably low serum FSH, LH and oestradiol concentrations have been published (Hall *et al*, *The Lancet*, **344**(8918):334-335 (1994)). Administration of r-hLH and hFSH caused E<sub>2</sub> levels to be raised, and the total number of follicles of 10 mm or more in diameter to be reduced, as compared to administration of hFSH alone. However, the number of large follicles remained sufficiently high to suggest an unacceptably high multiple pregnancy rate.

A further study compared the effect of administering r-hLH (at a dose of either 300 IU/day or 750 IU/day) and r-hFSH to normal ovulatory women after treatment with FSH for stimulating multiple follicular development prior to intrauterine implantation (Sullivan *et al*, *Journal of Clinical Endocrinology and Metabolism*, **84**, 228-232, 1999)). The results indicate that serum E<sub>2</sub> levels were raised in those women who received LH, although no measurements of the number and size of follicles were made and a multiple pregnancy occurred in the group receiving 750 IU/day of LH.

According to a first aspect of the present invention, there is provided the use of LH and/or a biologically-active analogue thereof in the production of a medicament for inducing folliculogenesis in anovulatory women at a daily dose in the range of from 100 to 1500 IU.

As used herein, an "IU ratio" is the ratio of the number of IU of one component to the number of IU of another component. It is noteworthy that gonadotrophins may now be expressed in (mass/ $\mu$ g) instead of biological IU. In this case, a conversion factor has to be used to translate the new value into IU. For convenience, references  
5 hereinafter to LH, FSH and hCG are intended to include biologically-active analogues thereof.

The inventors have found that the administration of LH at a dose of 100 to 1500 IU/day can promote paucifollicular development, that is to say, it can reduce the  
10 number of preovulatory follicles per treatment cycle in patients undergoing follicular induction, as compared to cycles where LH is not administered at a dose of 100 to 1500 IU/day. LH administered in accordance with the invention can induce unifolliculogenesis, i.e. the development of a single preovulatory follicle. Doses in the range of from 200 to 800 IU/day, and more preferably 225 to 450 IU/day, have been  
15 found to be particularly effective. The reduction in multifollicular development can reduce the number of cycles cancelled owing to excessive follicle development, i.e. it can rescue those cycles when there are an excessive number of follicles, making the process of ovulation induction more efficient. In addition, the incidence of multiple pregnancy and of OHSS can be reduced.

20 The required daily dose may be administered as a single dose each day. Thus, the medicament may be packaged so as to provide only the daily dose of LH, e.g. in a unit-dose container such as a vial. However, it is possible that LH may be administered on two or more occasions during the day - provided of course that total  
25 LH administered during the day equals the daily dose - and the medicament packaged accordingly, i.e. in a multi-dose container. It is also possible that LH could be administered on alternate days or at even longer intervals. Such decisions will be taken by the physician administering the medicament and will depend on parameters such as the patient's body mass index (BMI), medical history, stage of follicular

development when receiving LH, metabolism, response to the treatment, the half-life of the medicament and so on.

Folliculogenesis will generally be induced in anovulatory women by the administration of FSH using the conventional protocol or the chronic low dose protocol described above or an alternative protocol. LH should be administered at an appropriate stage of follicular development, e.g. the mid- to late-follicular phase. This stage may be decided by the physician administering the medicament and may depend on the regime by which ovulation is induced. By way of example, the appropriate stage of follicular development may be judged to have been reached when at least a single follicle reaches a mean diameter of 8 mm, or when at least one follicle has a mean diameter in the range 10-15 mm (preferably 11-14 mm), or when there are more than 3 follicles with a mean diameter in the range of from 8 to 13 mm and no larger follicles.

The administration of LH will generally cease when ovulation is induced by the administration of the high dose of hCG. Again, the timing of hCG administration to induce ovulation may be decided by the physician. For example, it may be when there is at least one follicle having a diameter of 18 mm or more and no more than 3, preferably 2, follicles having a diameter of 11 mm or more.

LH can be administered only when the required stage of follicular development has been reached. In this case, the administration of FSH can be discontinued altogether or can be continued at the same dose as before, or at a lower or higher dose. It is preferred if the administration of FSH is continued but at a lower dose than previously, the dose being lower than that of LH.

Alternatively, LH can be administered concomitantly with the conventional or chronic low dose protocols, i.e. prior to follicular development reaching an appropriate stage.

When the required stage of follicular development has been reached, the



administration of FSH can be discontinued or continued as before, or at a lower or higher dose, provided that LH is administered at the appropriate dose. In a further alternative, the medicament may be formulated such that it can be used in a procedure which replaces the conventional or chronic low dose protocols.

5

Thus, FSH and/or a biologically-active analogue thereof may be used in the production of the medicament. In this embodiment, the IU ratio of LH to FSH is preferably in the range of from 1.5:1 to 20:1. More preferably, the ratio is in the range of from 1.5:1 to 10:1.

10

When the medicament is for administration after the appropriate stage of follicular development has been reached, the IU ratio of LH:FSH may be about 10:1. A particularly preferred daily dose for such a medicament is 375 IU of r-hLH and 37.5 IU of r-hFSH.

15

According to a second aspect of the invention, there is provided the use of LH and FSH and/or biologically-active analogues thereof in the production of a medicament for inducing folliculogenesis in women at an IU ratio of LH to FSH in the range of from 1.5:1 to 20:1.

20

The uses of the first and second aspects of the invention may be modified in that LH is replaced by an equivalent dose of hCG and/or a biologically-active analogue thereof.

25

As used herein, an "equivalent dose" of human chorionic gonadotrophin (hCG) is calculated on the basis that 1 IU of hCG is equivalent to 5-7 IU of LH in the pharmacopoeia Van Hell bioassay (Van Hell, H, *et al*, Effects of human menopausal gonadotrophin preparations in different bioassay methods, *Acta Endocrin.*, 47: 409-418, 1964). For convenience, references herein to luteinising hormone (LH) are intended to include hCG, with doses of LH being intended to include the equivalent dose of hCG.

30

According to a third aspect of the invention, there is provided a product containing LH (or an equivalent dose of hCG) and FSH and/or biologically-active analogues thereof as a combined preparation for simultaneous, sequential or separate use in inducing  
5 folliculogenesis in women, the preparation comprising LH (or an equivalent dose of hCG) and FSH and/or biologically-active analogues thereof at an IU ratio of LH (hCG) to FSH in the range of from 1.5:1 to 20:1.

In accordance with the second and third aspects of the invention, LH or hCG and FSH  
10 may be administered to anovulatory women, preferably throughout the cycle up until the induction of ovulation by the administration of the high dose of hCG. Alternatively, they may be administered after follicular development has reached an appropriate stage.

15 The invention also provides a method for the induction of folliculogenesis in anovulatory women, including the administration of luteinising hormone and/or a biologically-active analogue thereof at a dose in the range of from 100 to 1500 IU/day or an equivalent dose of human chorionic gonadotrophin and/or a biologically-active analogue thereof.

20 LH, FSH and hCG may be obtained from natural sources, e.g. isolated from urine, pituitary or placenta, or may be obtained using recombinant DNA technology (see WO85/01959 and Loumaye *et al*, *Human Reprod.*, 11: 95-107, 1996). Biologically-active analogues thereof include peptidic analogues, non-peptidic analogues and  
25 chimeras. It is preferred if human LH and FSH are used in the present invention.

Compounds useful in the invention may be formulated for administration by any convenient route, often in association with a pharmaceutically and/or veterinarily acceptable carrier. It is preferred that the compounds are formulated for parenteral  
30 administration.

It is preferred that the LH and FSH (when present) be administered subcutaneously, preferably into the anterior abdominal wall.

5 Formulations for parenteral administration will usually be sterile. Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; aqueous and non-aqueous sterile suspensions which may include suspending agents and  
10 thickening agents are also within the scope of the invention. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile  
15 powders, granules and tablets. The formulations can be administered through a prefilled syringe, an auto-injector or a multidose auto-injector.

Oral and other enteral formulations need not be sterile and may be presented in unit- or multi-dose form. Oral formulations may be in the form of solids, such as powders,  
20 granules, tablets, capsules (for example hard or soft gelatin capsules) or lozenges, or liquids, such as syrups or elixirs. Fillers and/or carriers may be present as appropriate, and those skilled in the art of pharmaceutical formulation will be able to provide such additional or alternative excipients as may be necessary or desirable; flavouring agents are one example. Any formulation intended for oral administration may be formulated  
25 for enteric resistance, so as to assist delivery to the small intestine by avoiding or mitigating any digestion of the compound(s) as may occur in the stomach or the proximal part of the small intestine. Tablets or capsules may be enteric coated, for example by conventional procedures. Liquid formulations may be effectively rendered enteric resistant by including or being co-administered with a suitable agent such as medium-  
30 chain triglycerides.

Enteral compositions other than oral compositions include rectal compositions, which may be in the form of a suppository. Suppositories will generally include a suppository base, such as cocoa butter. Again, particular formulations containing the active  
5 ingredient(s) may routinely be prepared by those skilled in the art of pharmaceutical formulation.

Preferred features of each aspect of the invention are as for each other aspect, *mutatis mutandis*.

10 All patent and literature documents referenced throughout this specification are hereby incorporated by reference to the fullest extent allowed by law.

The invention will now be described further in the following non-limiting examples.

15 *Example 1*

The effect of LH when administered after FSH stimulation was examined on WHO Group II anovulatory women during a clinical study conducted according to ICH GCP  
20 (International Conference on Harmonisation – Good Clinical Practice) guidelines. The patients had the following characteristics:

Premenopausal; aged between 18 and 39; infertile due to ovulatory  
dysfunction; have had spontaneous menses, menses induced by clomiphene  
25 citrate therapy or a positive progestin-induced withdrawal bleed within the previous year; a body mass index of 35 or less (calculated as body weight in kg divided by (height x weight) in m<sup>2</sup>); euthyroid; no medical condition which may interfere with the absorption, distribution, metabolism or excretion of LH; no clinically systemic disease; no known allergy to gonadotrophin  
30 preparations; no persistent ovarian cyst of 11 mm or greater or ovarian

endometrioma (as determined by ultrasound); no previous or current hormone dependent tumour; no clinically relevant reproductive tract disease; and no active substance abuse.

- 5 The patients underwent routine ovulation induction with FSH until there were 4 or more follicles in the range of from 8-13 mm in diameter, no larger follicles and an endometrium of 8 mm or more thickness. They were then randomised into 3 blinded groups, one to receive a placebo, one to receive 225 IU/day of r-hLH and one to receive 450 IU/day of r-hLH.

10

Table 1 below summarises the respective groups of patients:

**Table 1**

Mean $\pm$ SD	Placebo	r-hLH 225 IU/day	r-hLH 450 IU/day
No of patients	5	4	8
Age (yrs) (min-max)	29.2 $\pm$ 5.7 (23-35)	26.8 $\pm$ 6.2 (20-35)	30.9 $\pm$ 3.9 (25-38)
Weight (kg) (min-max)	62.8 $\pm$ 15.9 (47-86)	60.0 $\pm$ 1.6 (58-62)	66.8 $\pm$ 15.4 (48-97)
BMI (min-max)	24.6 $\pm$ 4.7 (20-31)	22.8 $\pm$ 1.9 (21-25)	24.7 $\pm$ 4.9 (18-34)

- 15 r-hLH (LHadi ®, Serono) was used in vials containing 75 IU r-hLH and 47.75 mg of sucrose, phosphate buffer and Tween 20 in a lyophilised form. LHadi is produced in genetically engineered Chinese hamster Ovary (CHO) cells in which the genes encoding the alpha and beta chains of human LH have been introduced through recombinant technology. The specific activity of LHadi is approximately 15000 IU
- 20 LH/mg.

For a dose of 225 IU, 3 vials were used. One vial was reconstituted in 1 ml of water and gently agitated, taking care to avoid contact with the rubber stopper. The totality of the resulting solution was aspirated and used for reconstitution of the second vial. After gentle agitation, the totality of the resulting solution was aspirated and used for reconstitution of the third vial. After further gentle agitation, the totality of the resulting solution was aspirated and immediately injected subcutaneously in the anterior abdominal wall using a new needle. For a dose of 450 IU, two injections of 225 IU were made.

The placebo was in vials matching the r-hLH vials but containing only sucrose, phosphate buffer and Tween 20.

The r-hLH/placebo treatment was continued for 7 days unless at least one follicle reached a mean diameter of at least 18 mm and there were 3 or fewer follicles having a mean diameter of 11 mm or greater. In this case, a single dose of 5000 IU of u-hCG (Profasi ®, Serono) was given subcutaneously.

Prior to and during the r-hLH/placebo treatment, ultrasound (US) was used at intervals of 1-2 days to measure the mean diameter of the follicles (determined as the mean of the two longest perpendicular diameters) and the endometrial thickness (assessed as the distance from the hyperechogenic interface of the endometrium and the myometrium to the opposite interface including the stronger midline echo (endometrial interface)). All follicles with a mean diameter of 11 mm or greater were recorded.

Prior to and each time an ultrasound scan was carried out during the r-hLH/placebo treatment, a blood sample was taken and the resulting serum was analysed for E<sub>2</sub> (oestradiol), P<sub>4</sub> (progesterone), LH, FSH and androstenedione.

E<sub>2</sub> and P<sub>4</sub> were analysed using DPC Coat-a-count, RIA solid phase coated tube

separation, LH (serum and urinary) and FSH were analysed using MAIACLONE IRMA, and androstenedione was analysed using Diagnostic System Laboratories method, RIA.

5       The results are summarised in Tables 2-4 and in Figure 1 of the accompanying drawings which is a graph showing the size and number of follicles on the day of hCG administration (or the last day of treatment of no hCG was administered) for each of the patients.

10       It can be seen that the administration of LH at 225 or 450 IU/day subsequent to FSH treatment resulted in a more marked follicular regression than in the administration of placebo, as suggested by patients with complete follicular regression, a smaller number of follicles on the day of hCG administration and a reduction in follicle median size from 15 mm in the placebo group to 14 mm in the 225 IU r-hLH group  
15       and 13 mm in the 450 IU r-hLH group.

The efficacy of r-hLH in promoting mono-ovulation is illustrated by the emergence of a dominant follicle (as evidenced by the median size), the absence of follicular phase luteinisation and a comparatively lower P<sub>4</sub> level at the mid-luteal phase.

20

#### *Example 2*

The effect of LH and FSH administered during the late follicular phase was examined on WHO Group I anovulatory women during a clinical trial conducted according to  
25       ICH GCP guidelines. The patients had the following characteristics:

premenopausal; aged between 18 and 39; a clinical history of  
hypogonadotrophic hypogonadism; have stopped treatment (if any) with  
pulsatile GnRH, gonadotrophins or oestrogen progesterone treatment therapy at  
30       least one month before the screening procedure; have had a negative

progesterone challenge test performed during the screening period; had the following hormonal values in a fasting blood sample (between 7 and 9.30 AM) drawn within 6 months before the treatment period:

5	FSH:	< 5 mIU/ml
	LH:	< 1.2 mIU/ml
	Thyroid stimulating hormone (TSH):	< 6.5 $\mu$ IU/ml
	Free T <sub>4</sub> :	>11 and < 24 pmol/l
	Testosterone:	< 3.5 nmol/l
10	Prolactin (PRL):	< 520 mIU/l;

no clinically significant abnormal finding, within 6 months prior to study start, in pre-treatment haematology, in clinical chemistry and urinalysis parameters or results of no pathological significance of outside normal limits; have, on file, if clinically indicated, a CT scan or MRI of the hypothalamic pituitary region to document current putative tumoral status of the region; a body mass index of between 18.4 (percentile 10 for 18 years) and 31.4 (percentile 90 for 38 years); no medical condition which may interfere with the absorption, distribution, metabolism or excretion of LH or FSH; no clinically systemic disease; no known allergy to gonadotrophin preparations; no persistent ovarian cyst of 11 mm or greater or ovarian endometrioma (as determined by ultrasound); no previous or current hormone dependent tumour; no clinically relevant reproductive tract disease; and no active substance abuse.

The study was divided into an open phase of a maximum of 28 days and a blinded phase of a maximum of 7 days.

In the open phase, all patients received 225 IU/day of r-hLH and 112.5 IU/day of r-hFSH. If there was no rise in E<sub>2</sub> levels or sign of follicular growth after 7 days, the dose of r-hFSH was raised to 150 IU/day. After a further 7 days, the dose of r-hFSH



was raised to 187.5 IU/day if there was no rise in E<sub>2</sub> levels or sign of follicular growth and after a further 7 days, the dose of r-hFSH was raised to 262.5 IU/day if there was no rise in E<sub>2</sub> levels or sign of follicular growth. The dose of r-hLH remained constant throughout the open phase.

5

When a patient had at least one follicle with a mean diameter in the range of from 10-13 mm, she entered the blinded phase. In this phase, the patients were randomised into 3 blinded groups, one to receive a LH placebo and continue the dose of r-hFSH received on the last day of the open phase, one to receive 225 IU/day of r-hLH and continue the dose of r-hFSH received on the last day of the open phase, and one to receive 225 IU/day of r-hLH and a FSH placebo.

10

Table 5 below summarises the respective groups of patients.

15

**Table 5**

Mean±SD	FSH/Placebo	r-hLH/placebo	FSH/r-hLH
No of patients	6	6	8
Age (yrs) (min-max)	31.9 ± 6.2 (21-39)	31.0 ± 3.0 (27-34)	30.8 ± 4.6 (25-37)
Weight (kg) (min-max)	70.3 ± 10.0 (60-88)	51.7 ± 4.4 (46-59)	66.9 ± 15.9 (50-89)
BMI (min-max)	25.2 ± 2.3 (21-28)	19.8 ± 1.1 (19-21)	24.6 ± 4.3 (20-30)

r-hFSH (Gonal-F ®, Serono) was used in ampoules containing 75 IU r-hFSH and 30 mg sucrose and phosphate buffer in a lyophilised form, up to 3 of which were dissolved in 1 ml of water for injection. Matching ampoules containing only sucrose and phosphate buffer were provided for the FSH placebo.

20

r-hLH (LHadi ®, Serono) was provided and administered as in Example 1. The LH placebo was in vials matching the r-hLH vials but containing only sucrose, phosphate buffer and Tween 20.

5

All injections were made subcutaneously into the anterior abdominal wall.

The blinded phase was continued for 7 days unless at least one follicle reached a mean diameter of at least 18 mm and there were 2 or fewer follicles having a mean diameter of 11 mm or greater. In this case, a single dose of 10000 IU of u-hCG (Profasi ®, Serono) was given subcutaneously.

10

On the first, fifth and eight days of the open phase, and at regular intervals (i.e. 1 to 2 days) during the blinded phase, ultrasound was used to measure the mean diameter of the follicles and the endometrial thickness. All follicles with a mean diameter of 11 mm or greater were recorded.

15

On the first day of the open phase, and at regular intervals (i.e. 1 to 2 days) during the blinded phase, a blood sample was taken and the resulting serum was analysed for E<sub>2</sub>, P<sub>4</sub>, LH, FSH and androstenedione as in Example 1.

20

The results are summarised in Tables 6-9 and in Figure 2 of the accompanying drawings which is a graph showing the size and number of follicles on the day of hCG administration (or the last day of treatment of no hCG was administered) for each of the patients.

25

It can be seen that stopping FSH and administering r-hLH at 225 IU/day resulted in a marked and excessive follicular regression.

30

The efficacy of r-hLH in promoting mono-ovulation in the presence of FSH is

illustrated by a reduction in the mean number of follicles having a diameter of 14 mm or greater, an increase in the proportion of patients with only 1 or 2 follicles having a diameter of 14 mm or greater, the emergence of a dominant follicle (as evidenced by a median follicle size of 12 mm as compared to 15 mm for the FSH/placebo group), and  
5 the absence of follicular phase luteinisation.

Table 2 – Summary Data on Number and Size of Follicles and hCG Cancellation

Treatment Group	Patient Id	Number of Follicles $\geq 8$ mm at Baseline	Number of Follicles $\geq 11$ mm Last US	Number of Follicles $\geq 14$ mm Last US	hCG Received	Reason / Comment
Placebo	20002	8	5	4	No	Risk of OHSS
	30003	22	14	10	Yes	
	40001	20	3	2	Yes	
	<sup>P</sup> 40005	12	3	1	Yes	
	<sup>P</sup> 40008	8	3	2	Yes	
	N = 5	14.00 $\pm$ 6.63	5.60 $\pm$ 4.77	3.80 $\pm$ 3.63	4 Yes/1 No	
r-hLH 225 IU/day	20001	5	1	0	No	Follicles regressed
	30001	12	0	0	No	Failure of treatment
	40003	18	5	2	Yes	
	40007	4	3	3	Yes	
	N = 4	9.75 $\pm$ 6.55	2.25 $\pm$ 2.22 $p=0.4391$	1.25 $\pm$ 1.50 $p=0.2342$	2 Yes/2 No	
r-hLH 450 IU/day	10001	6	0	0	No	all follicles became atretic
	20003	10	13	4	No	Risk of OHSS
	30002	9	5	3	No	Failure of treatment
	40002	17	3	1	Yes	
	40004	7	3	1	Yes	
	40009	4	3	2	Yes	
	50001	9	0	0	No	Failure of treatment
	70001	9	3	1	Yes	
	N = 8	8.88 $\pm$ 3.83	3.75 $\pm$ 4.10 $p=0.8684$	1.50 $\pm$ 1.41 $p=0.2731$	4 Yes/4 No	

*p-values from comparison with placebo group (ANCOVA adjusted for number of follicles at baseline)*

<sup>P</sup>: pregnant patient

**Table 3 - Number of Patients with 0, 1, 2, 3 or >3 Follicles on the Day of hCG or on the Last Day of Treatment if No hCG was Administered**

		Treatment Randomised						p-values				
		Placebo		r-hLH 225 IU/day		r-hLH 450 IU/day		Contrast**	One-sided		Two-sided	
		N	%	N	%	N	%		Asymptotic	Exact	Asymptotic	Exact
Follicles >= 11 mm	0 foll. >=11mm	0	0.0%	1	25.0%	2	25.0%	Placebo vs. r-hLH 225 IU Placebo vs. r-hLH 450 IU r-hLH 225 IU vs. r-hLH 450 IU Overall comparison	0.0562	0.1429	0.1124	0.1746
	1 foll. >=11 mm	0	0.0%	1	25.0%	0	0.0%		0.1108	0.2339	0.2217	0.3590
	2 foll. >=11 mm	0	0.0%	0	0.0%	0	0.0%		0.2987	0.3879	0.5973	0.7192
	3 foll. >=11 mm	3	60.0%	1	25.0%	4	50.0%		0.2064	0.2222	0.4128	0.4378
	>3 foll. >=11 mm	2	40.0%	1	25.0%	2	25.0%					
	All	5	100.0%	4	100.0%	8	100.0%					
	Follicles >= 14 mm	0 foll. >=14mm	0	0.0%	2	50.0%	2	25.0%	Placebo vs. r-hLH 225 IU Placebo vs. r-hLH 450 IU r-hLH 225 IU vs. r-hLH 450 IU Overall comparison	0.0774	0.1429	0.1547
1 foll. >=14 mm		1	20.0%	0	0.0%	3	37.5%	0.0817		0.1298	0.1635	0.2416
2 foll. >=14 mm		2	40.0%	1	25.0%	1	12.5%	0.3786		0.4788	0.7572	0.8323
3 foll. >=14 mm		0	0.0%	1	25.0%	1	12.5%	0.1259		0.1354	0.2519	0.2675
>3 foll. >=14 mm		2	40.0%	0	0.0%	1	12.5%					
All		5	100.0%	4	100.0%	8	100.0%					

Contrast \*\* Overall Comparison: Jockheere-Terpstra test  
Pairwise Comparison: Cochran-Armitage test for trend.

**Table 4 – Descriptive Statistics of Hormone Levels**  
**Measured at T1 and on the Day of hCG or on the Last Day of Treatment if No hCG was Administered**

Variable	Treatment	T1 (first day of stimulation)						Day of hCG or last day of treatment if no hCG was administered					
		n	Mean	SD	SEM	Median	Range	n	Mean	SD	SEM	Median	Range
FSH (IU/L)	Placebo	5	12.20	5.60	2.50	9.50	(8-21)	5	6.54	3.84	1.72	7.90	(2-11)
	r-hLH 225 IU/day	4	12.53	6.75	3.37	11.45	(6-21)	4	7.35	2.98	1.49	6.05	(6-12)
	r-hLH 450 IU/day	7	11.10	3.71	1.40	9.80	(8-19)	8	6.94	2.05	0.73	6.25	(5-10)
	All	16	11.80	4.84	1.21	9.65	(6-21)	17	6.92	2.70	0.66	6.20	(2-12)
LH (IU/L)	Placebo	5	7.84	6.30	2.82	4.80	(3-18)	5	6.12	2.74	1.23	6.90	(2-9)
	r-hLH 225 IU/day	4	5.25	2.69	1.34	6.20	(1-7)	4	6.80	4.48	2.24	6.40	(2-12)
	r-hLH 450 IU/day	7	4.60	4.14	1.57	3.40	(1-13)	7	6.67	4.14	1.56	4.80	(3-15)
	All	16	5.78	4.58	1.15	4.55	(1-18)	16	6.53	3.60	0.90	6.00	(2-15)
E2 (pmol/L)	Placebo	5	4031.6	3759.9	1681.5	3612.0	(598-10017)	5	4780.6	4612.7	2062.9	3540.0	(313-11040)
	r-hLH 225 IU/day	4	1491.8	1633.5	816.8	851.5	(384-3880)	4	2560.0	4715.7	2357.8	227.0	(153-9633)
	r-hLH 450 IU/day	7	1376.7	885.8	334.8	1315.0	(123-2809)	8	1966.9	2665.1	942.3	297.0	(133-7269)
	All	16	2235.1	2486.8	621.7	1304.5	(123-10017)	17	2934.0	3763.6	912.8	378.0	(133-11040)
P4 (nmol/L)	Placebo	5	4.56	1.80	0.80	4.30	(3-7)	5	8.86	10.83	4.84	4.50	(2-28)
	r-hLH 225 IU/day	4	3.08	1.02	0.51	3.05	(2-4)	4	2.68	1.15	0.57	2.50	(2-4)
	r-hLH 450 IU/day	7	2.47	1.03	0.39	2.30	(1-4)	8	2.89	1.73	0.61	2.25	(1-6)
	All	16	3.28	1.53	0.38	2.85	(1-7)	17	4.59	6.24	1.51	2.80	(1-28)
Androstenedione (nmol/L)	Placebo	5	17.42	11.62	5.20	16.50	(5-35)	5	15.74	7.03	3.14	14.40	(8-27)
	r-hLH 225 IU/day	4	8.63	0.88	0.44	8.30	(8-10)	4	11.75	1.92	0.96	12.00	(9-14)
	r-hLH 450 IU/day	7	10.53	7.11	2.69	8.00	(5-26)	8	12.18	9.56	3.38	8.95	(6-35)
	All	16	12.21	8.38	2.09	9.10	(5-35)	17	13.12	7.49	1.82	11.40	(6-35)

Table 6 - Summary Data on Stimulation Open and Blinded Phases and hCG Cancellation

Treatment Group	Patient Id	First Dose of FSH (IU)	Last Dose of FSH (IU)	Number of Days	Cumulative FSH Dose	Cumulative LH Dose	Number of Days	Cumulative FSH Dose	Cumulative LH Dose	hCG Received
Gonal-F/Placebo	10002	112.5	112.5	8	900	1800	2	225		No
	10004	112.5	150.0	13	1688	2925	3	450		No
	20001	112.5	112.5	7	788	1575	3	338		No
	30002	112.5	150.0	10	1238	2250	1	150		Yes
	40002	112.5	150.0	13	1688	2925	2	300		Yes
	50001	112.5	112.5	7	788	1575	5	563		Yes
	N=6	112.5	131.3±20.5	9.7±2.8	1181.3±425.4	2175.0±631.1	2.7±1.4	337.5±150.0		3 Yes/3 No
	10003	112.5	150.0	15	1988	3375	3	675		No
	10005	112.5	112.5	2	225	450	5	1125		No
	30003	112.5	112.5	7	788	1575	7	1575		No
r-hLH/Placebo	40001	112.5	112.5	7	788	1575	5	1125		Yes
	50002	112.5	112.5	5	563	1125	7	1575		No
	60002	112.5	150.0	12	1538	2700	4	900		Yes
	N=6	112.5	125.0±19.4	8.0±4.7	981.3±654.9	1800.0±1064.9	5.2±1.6	1162.5±360.5		2 Yes/4 No
	10001	112.5	187.5	17	2363	3825	3	563		Yes
	10006	112.5	112.5	3	338	675	2	225		No
	20002	112.5	112.5	11	1238	2475	1	113		Yes
	40003	112.5	112.5	7	788	1575	3	338		Yes
	40004	112.5	112.5	7	788	1575	2	225		Yes
	50003	112.5	112.5	6	675	1350	7	788		No
Gonal-F/r-hLH	60001	112.5	112.5	6	675	1350	2	225		No
	N=8	112.5	126±27.9	8.5±4.3	1031.3±632.0	1912.5±977.1	2.9±1.8	365.6±223.0		5 Yes/3 No

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**Table 8 – Number of Patients with 0, 1, 2, 3 or >3 Follicles on the Day of hCG or on the Last Day of Treatment if No hCG was Administered**

Treatment Randomised										Contrast**	p-values			
Variable	Number of Follicles	Gonal-F Placebo		r-hLH Placebo		Gonal-F/r- hLH		One-sided			Two-sided			
		N	%	N	%	N	%	Asymptotic	Exact		Asymptotic	Exact		
Follicles ≥11mm	0 foll. ≥ 11mm	0	0.0%	2	33.3%	1	12.5%	Gonal-F/Placebo vs r-hLH/placebo	0.0057	0.0141	0.0115	0.0281		
	1 foll. ≥ 11 mm	0	0.0%	2	33.3%	0	0.0%	Gonal-F/Placebo vs Gonal-F/r-hLH	0.0820	0.1538	0.1641	0.2887		
	2 foll. ≥ 11 mm	0	0.0%	0	0.0%	1	12.5%	r-hLH/Placebo vs Gonal-F/r-hLH	0.0399	0.0653	0.0799	0.1016		
	3 foll. ≥ 11 mm	1	16.7%	1	16.7%	2	25.0%	Overall comparison	0.2051	0.2184	0.4101	0.4325		
	> 3 foll. ≥ 11 mm	5	83.3%	1	16.7%	4	50.0%							
	All	6	100.0%	6	100.0%	8	100.0%							
Follicles ≥14mm	0 foll. ≥ 14mm	0	0.0%	4	66.7%	1	12.5%	Gonal-F/Placebo vs r-hLH/placebo	0.0046	0.0076	0.0092	0.0152		
	1 foll. ≥ 14 mm	1	16.7%	1	16.7%	4	50.0%	Gonal-F/Placebo vs Gonal-F/r-hLH	0.0424	0.0766	0.0848	0.1485		
	2 foll. ≥ 14 mm	2	33.3%	1	16.7%	2	25.0%	r-hLH/Placebo vs Gonal-F/r-hLH	0.0461	0.0776	0.0922	0.1575		
	3 foll. ≥ 14 mm	1	16.7%	0	0.0%	0	0.0%	Overall comparison	0.1330	0.1377	0.2660	0.2769		
	> 3 foll. ≥ 14 mm	2	33.3%	0	0.0%	1	12.5%							
	All	6	100.0%	6	100.0%	8	100.0%							

Contrast \*\*

Overall Comparison: Jonckheere-Terpstra test  
Pairwise Comparison: Cochran-Armitage test for trend

**Table 9 – Descriptive Statistics of Hormone Levels Measured at T1 and on the Day of hCG or on the Last Day of Treatment if No hCG was Administered**

Variable	Treatment	T1 (first day of stimulation)						Day of hCG or last day of treatment if no hCG was administered					
		n	Mean	SD	SEM	Median	Range	n	Mean	SD	SEM	Median	Range
FSH (IU/L)	Gonal-F/Placebo	6	8.58	3.19	1.30	8.05	(5-14)	5	8.52	3.13	1.40	7.00	(5-12)
	r-hLH/Placebo	6	12.37	6.73	2.75	9.85	(9-26)	6	3.33	2.13	0.87	3.00	(1-6)
	Gonal-F/r-hLH	8	9.68	3.44	1.22	10.15	(4-15)	8	9.03	2.66	0.94	9.55	(4-13)
	All	20	10.16	4.62	1.03	9.75	(4-26)	19	7.09	3.62	0.83	7.00	(1-13)
LH (IU/L)	Gonal-F/Placebo	6	1.08	0.16	0.07	1.00	(1-1)	5	1.00	0.00	0.00	1.00	(1-1)
	r-hLH/Placebo	6	1.30	0.60	0.24	1.00	(1-3)	6	1.88	1.56	0.64	1.25	(1-5)
	Gonal-F/r-hLH	8	1.58	0.87	0.31	1.10	(1-3)	8	1.56	0.71	0.25	1.35	(1-3)
	All	20	1.35	0.65	0.15	1.00	(1-3)	19	1.52	1.00	0.23	1.00	(1-5)
E2 (pmol/L)	Gonal-F/Placebo	6	691.50	737.24	300.98	474.5	(160-2171)	5	725.80	989.66	442.59	302.00	(163-2483)
	r-hLH/Placebo	6	669.33	483.03	197.20	630.00	(129-1311)	6	116.33	102.12	41.69	100.00	(33-316)
	Gonal-F/r-hLH	8	1416.50	1666.01	589.02	650.00	(187-4885)	7	3452.86	3843.18	1452.59	1537.00	(251-11257)
	All	20	974.85	1167.89	261.15	474.50	(129-4885)	18	1583.17	2803.84	660.87	309.00	(33-11257)
P4 (nmol/L)	Gonal-F/Placebo	6	1.4	0.6	0.2	1.1	(1-2)	5	1.6	0.8	0.4	1.3	(1-3)
	r-hLH/Placebo	6	2.1	1.1	0.4	1.6	(1-4)	6	1.9	1.5	0.6	1.2	(1-5)
	Gonal-F/r-hLH	8	2.3	1.3	0.5	2.0	(1-5)	7	22.9	53.0	20.0	2.8	(2-143)
	All	20	2.0	1.1	0.2	1.6	(1-5)	18	10.0	33.2	7.8	1.9	(1-143)
Androstenedione (nmol/L)	Gonal-F/Placebo	6	4.87	2.55	1.04	3.65	(3-10)	4	4.08	2.35	1.18	3.20	(2-8)
	r-hLH/Placebo	6	5.93	2.50	1.02	5.65	(3-9)	6	5.63	2.37	0.97	5.15	(3-10)
	Gonal-F/r-hLH	8	7.71	3.78	1.34	7.30	(3-14)	8	10.58	6.19	2.19	10.80	(3-22)
	All	20	6.33	3.19	0.71	5.85	(3-14)	18	7.48	5.18	1.22	5.90	(2-22)

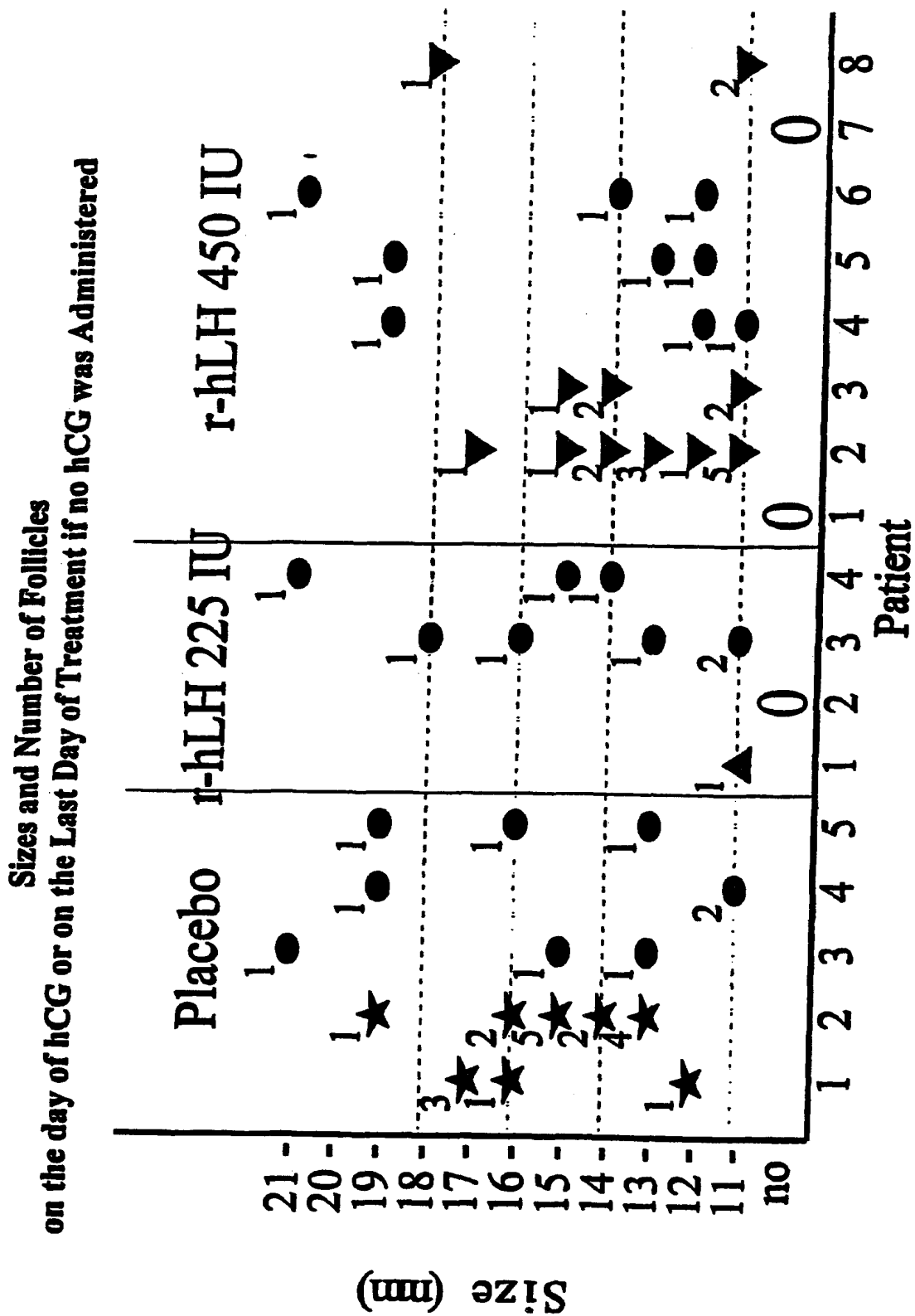
## CLAIMS

1. The use of LH and/or a biologically-active analogue thereof in the production of a medicament for inducing folliculogenesis in anovulatory women at a daily dose in the range of from 100 to 1500 IU.
2. The use as claimed in claim 1, wherein the LH is r-hLH.
3. The use as claimed in claim 1 or claim 2, wherein the daily dose is in the range of from 200 to 800 IU.
4. The use as claimed in claim 3, wherein the daily dose is in the range of from 225 to 450 IU.
5. The use as claimed in any preceding claim, wherein FSH and/or a biologically-active analogue thereof is used in the production of the medicament.
6. The use as claimed in claim 5, wherein the IU ratio of LH to FSH is in the range of from 1.5:1 to 20:1.
7. The use as claimed in claim 6, wherein the ratio is in the range of from 1.5:1 to 10:1.
8. The use of LH and FSH and/or a biologically-active analogues thereof in the production of a medicament for inducing folliculogenesis in women at an IU ratio of LH to FSH in the range of from 1.5:1 to 20:1.
9. The use as claimed in claim 8, wherein the medicament is for inducing folliculogenesis in women at a daily dose of LH in the range of from 100 to 1500 IU.

10. The use as claimed in any preceding claim, modified in that LH and/or a biologically-active analogue thereof is replaced by an equivalent dose of hCG and/or a biologically-active analogue thereof.
- 5 11. The use as claimed in any preceding claim, wherein the medicament is for inducing paucifolliculogenesis or unifolliculogenesis in women.
- 10 12. A product containing LH (or an equivalent dose of hCG) and FSH and/or biologically-active analogues thereof as a combined preparation for simultaneous, sequential or separate use in inducing folliculogenesis in women, the preparation comprising LH (or an equivalent dose of hCG) and FSH and/or biologically-active analogues thereof at an IU ratio in the range of from 1.5:1 to 20:1.
- 15 13. A product as claimed in claim 12, wherein the ratio is in the range of from 1.5:1 to 20:1.
14. A product as claimed in claim 13 wherein the ratio is in the range of from 1.5:1 to 10:1.
- 20 15. A product as claimed in claim 12, 13 or 14, which comprises 375 IU of r-hLH (or an equivalent dose of hCG) and 37.5 IU of r-hFSH
16. A product as claimed in any one of claims 12, 13 or 14, which is for inducing paucifolliculogenesis or unifolliculogenesis in women.

1/2

FIGURE 1



# **Individual Size and Number of Follicles on the Day of hCG or the Last US if no hCG was Administered**

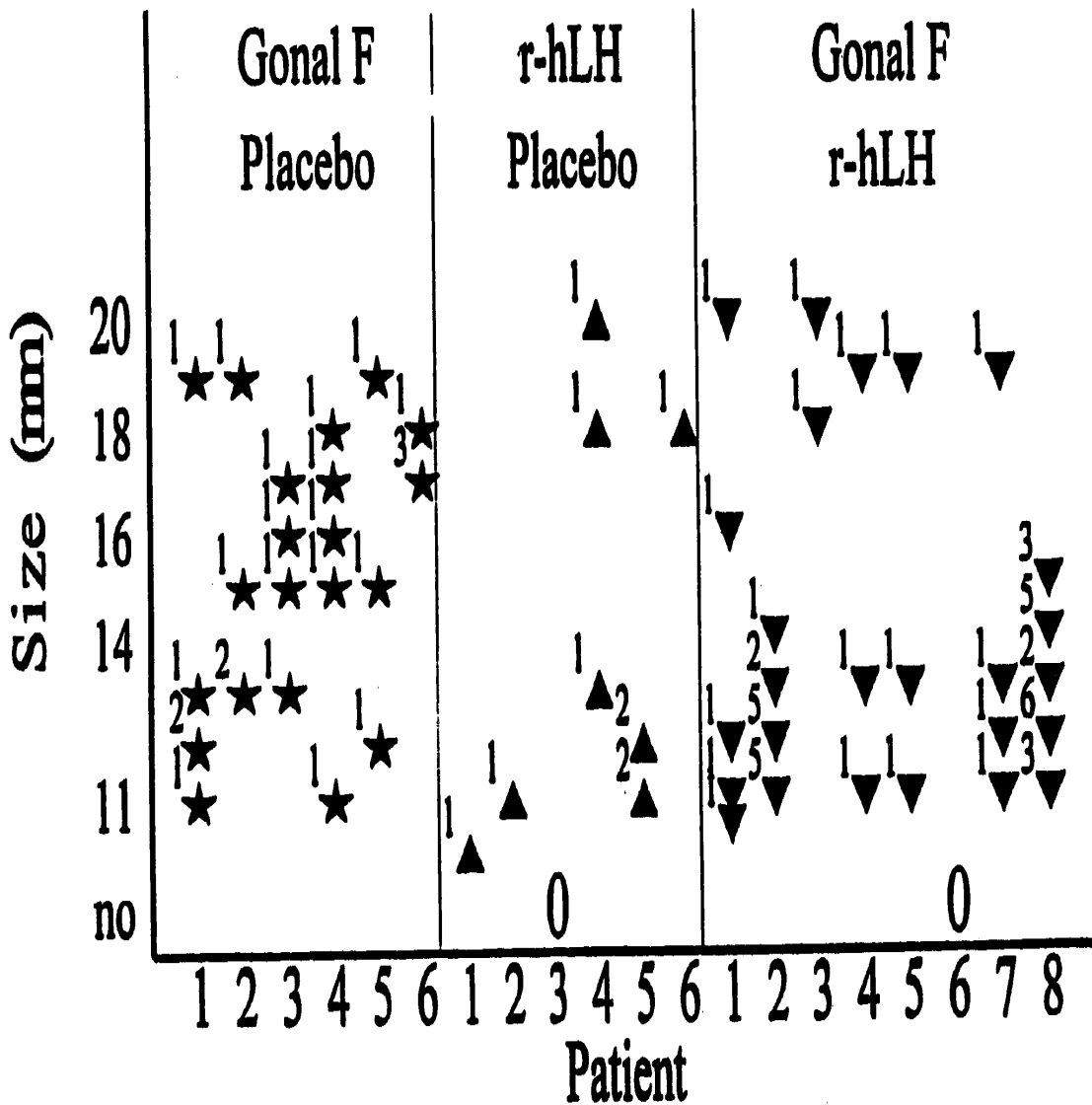


FIGURE 2

2/2

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01745

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/24 A61P15/08

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, MEDLINE, BIOSIS, LIFESCIENCES, CHEM ABS Data, EMBASE, SCISEARCH

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	<p>EUROPEAN RECOMBINANT HUMAN LH STUDY GROUP:  "Recombinant human luteinizing hormone (LH) to support recombinant human follicle-stimulating hormone (FSH)-induced follicular development in LH- and FSH-deficient anovulatory women: A dose-finding study."  JOURNAL OF CLINICAL ENDOCRINOLOGY &amp; METABOLISM,  vol. 83, no. 5, May 1998 (1998-05), pages 1507-1514, XP000891973  * Treatment Protocol, page 1508 *  the whole document</p>	<p>1-9,  11-14, 16</p>
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

28 June 2000

Date of mailing of the international search report

04/07/2000

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## INTERNATIONAL SEARCH REPORT

Inte. lional Application No

PCT/GB 00/01745

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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